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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,693	05/31/2001	Mark J. Cooper	003659.00009	6189

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/867,693	Cooper
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Nov 1, 2002 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-181 is/are pending in the application.

4a) Of the above, claim(s) 1, 8, 10-19, 28, 38-46, 48, 50, 53, 54, 57-68, 74, 79, 84, 86, 111-127, 160-163, 165-176 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 2-7, 9, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 69-73, 75-78, 80-83, 85, 87-110, 112-126, 128-159, 164, 177-186 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3 and 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election of Group II claims, Claims 2, 20, 29, 32, 35, 47-58, 103, 116, 131, 139, 147, 154, 164, and claims dependent there from, and of the species of acetate, polylysine with a cystein residue, and 23 nm, in the response filed November 1, 2002 is acknowledged. Because applicant did not distinctly and specifically point out the supposed error in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The species restriction between acetate and chloride as counter ions have been vacated by the examiner because the prior art search has been done and no undue burden was found to examine both species.

Claims 1, 8, 10-19, 28, 38-46, 48, 50, 53, 54, 57-68, 74, 79, 84, 86-102, 111, 127, 160-163, 165-176 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention and non-elected species.

Claims 2-7, 9, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 69-73, 75-78, 80-83, 85, 103-110, 112-126, 128-159, 164, and 177-181 are readable on the claimed invention and/or elected species, and thus, are pending for examination.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 20, 29, 32, 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "whichever is larger" because it is not apparent as to what is exactly the "whichever" refers to, nor is it apparent as to what is exactly the limitations when read the entire claim in view of the phrase, particularly when read in the context of the Markush group as writtenin the claims. Clarification is requested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 3, 5-7, 9, 20-21, 23-27, 29, 30, 32-36, 47, 49, 51, 55, 69-73, 75-78, 80-83, 85, 103, 104, and 164, readable on a compacted and spherical condensed polylysine/DNA complex comprising a single nucleic acid with a diameter of less than 23 nm and further comprising an ion of acetate, wherein the charge ratio is of about 1:1, and wherein the polylysine has not been modified at its N-terminal to incorporate a cystein residue, are

rejected under 35 USC 102(e) as being anticipated by, or in the alternative, under 35 USC 103(a) as being unpatentable over Hanson *et al.* (US Pat No. 5,844,107).

Hanson teaches a compacted and spherical condensed polylysine/DNA complex comprising a single nucleic acid with a diameter of less than 23 nm and further comprising an ion of acetate, wherein the charge ratio is of about 1:1, and wherein the polylysine has not been modified at its N-terminal to incorporate a cystein residue, *e.g.,* see abstract, claims 1-28, column 5, lines 5-10, column 16, lines 12-18, column 19, lines 37-47, lines 60-63, column 20, lines 7-19, column 21 bridging column 22, column 22, lines 35-42 regarding the recognition the prior art regarding the need of using acetate ions for increasing affinity of polylysine to DNA and/or condensation, column 23, lines 37-45 regarding the molar concentration of the salt (NaCl) employed and/or the charged ratio of about 4:1 to 1:4, claim 1 regarding the charged ratio of 1:1 and the spherical condensed complex, and Table 104 regarding the length of an employed polylysine, 15-56 lysine residues. Regarding the necessity of employing a salt and/or ions thereof so as to influence the affinity of polylysine and/or condensed status of the DNA/polylysine complex, the prior art provides descriptive details including working examples and tables so as to show that polylysine at an appropriate length and/or additions of salts and ions thereof can be incorporated and examined for the desired influence on the complex as intended by the teaching of the Hanson reference, *e.g.,* stability, level of compaction, shapes of the complexes, aggregation. As such, the claims are anticipatory, or in the alternative, was *prima facie* obvious over the prior art.

Claims 2-7, 9, 20-27, 29-37, 47, 49, 51, 52, 55, 56, 69-73, 75-78, 80-83, 85, 103-110, 112-126, 128-159, 164, and 177-181, readable on a further incorporation of a PEG (MW of 5 or 10 KD) to the polylysine with the length of 15-60 lysine residues wherein a cystein has been incorporated to the N-terminal of the polylysine so as to provide a bridge for attachment to the PEG, are rejected under 35 USC 103(a) as being unpatentable over Hanson taken with Park *et al.* (US Pat No. 6,177,274), Schacht (WO 98/19710), and further in view of either Serres *et al.* (Langmuir, 15, 6956-6960, 1999) or Lollo (WO 97/30731).

The rejection of the base claims on the basis of the teaching provided by Hanson is applied here as indicated above. Hanson does not teach the use of a PEG linked to a modified polylysine via a cystein residue,

nor does Hanson teach the MW of the PEG as being 5 KD or 10 KD.

However, at the time the invention was made, the concept of utilizing a polycationic polylysine (PLL) linked to PEG, whereby PEG-PLL functions as an enhanced linker so as to link the backbone of PLL to a bioactive molecule or targeting ligand and to subsequently enhance the stability and targeting efficiency of the bioactive molecule or the ligand to a cell of interest is well-taught in both Park (columns 3 and 4), and the Schacht reference (pages 9 and 10). Also, Park *et al.* teach on columns 2 through 3 that PLL (polylysine) has been routinely employed as a condensing agent so as to increase intracellular delivery of a charged agent, and that PEG of MW 0.5-20 K MW linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell (column 3 through column 4).

It would have been obvious for one of ordinary skill in the art to have further linked any PEG with MW of 5 or 10 KD to one or more polycationic agent such as polylysine having more than at least between 15 and 60 residues with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to have incorporated any known PEG species to a polycationic moiety(s) contained in the DNA complex of Hanson because the concept of utilizing a polycationic polylysine (PLL) linked to PEG, whereby PEG-PLL functions as an enhanced linker so as to link the backbone of PLL to a bioactive molecule or targeting ligand and to subsequently enhance the stability and the targeting efficiency of the bioactive molecule or the ligand to a cell of interest is well-taught in Park, and because both the Shacht and Park references teach that PEG linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell.

Insofar as the limitation of an incorporation a reactive group such as a cystein residue at the N-terminal of the polylysine, which terminal is further linked to a protective hydrophilic polymer such as PEG, the use of any reactive group including the use of a disulfide bond from any well-known source, *e.g.,* cystein, is also taught in the Schacht reference, page 3 bridging page 4, and page 26. It would have been obvious for one of ordinary skill in the art to have further modified the N-terminal of the polylysine by providing a disulfide bridge so as to act as bridge for PEG 's linkage. One of ordinary skill in the art would have been motivated to employ a cystein, which is well-known in the art as a source of a disulfide bond

used as an attachment point or a reactive group because such use of any reactive group including the use of a disulfide bond from any source is also taught in the Schacht reference.

Insofar as the limitation of a further addition of a counter ion to the complex so as to enhance the compaction of the DNA and/or complex and/or prevent aggregation of the DNA, Serres also teaches that polycationic polymers having counter ions such as Cl^- incorporated within which would not only to be able to complex with a desired DNA, but also lead to a stable and compacted DNA. In addition, Lollo further teaches the necessity of employing salts and/or counter ions (any ion capable of neutralizing a portion of the positive charge of cationic carrier molecules (by deprotonation) so as to enhance the inhibition of the aggregation of the carrier molecules. As such, the combined cited references further in view of either Serres or Lollo do teach, suggest, and provide a motivation for a person of ordinary skill in the art of polycationic-DNA complex based gene transfer to employ an appropriate amount of PEG-cystein-polylysine, wherein MW of PEG is 5 or 10 Kd, length of polylysine is between 15-60 residues and contains a modified disulfide bond at its N-terminal, and a counter ion such as acetate or chloride so as to enhance not only the transfection and compaction of the DNA contained in the complex but also the stability of the DNA during an *in vivo* circulation and/or an cell transfection process.

Thus, the claimed invention was as a whole *prima facie* obvious over the prior art of record.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER